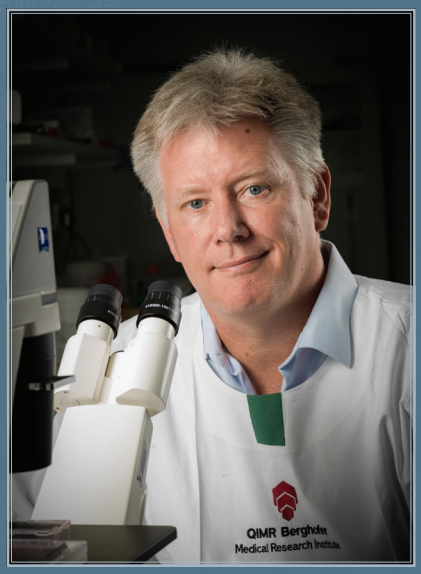
It Takes a Village

Professor Mark Smyth, Ph.D., Senior Scientist in the QIMR Berghofer Medical Research Institute in Brisbane, Australia, has a track record in the field of cancer immunology that is both impressive and wide-ranging. He has made fundamental discoveries in understanding how natural killer (NK) cells destroy tumors, his work has helped revitalize the concept of immune surveillance, and his preclinical studies of cancer immunotherapies have been translated into man. Undoubtedly modest, Smyth credits part of his success to an international network of close collaborators—friends, in fact—through which his science has been enriched and magnified.



(Photo: Courtesy of M. Smyth)

Mark Smyth, Ph.D.

On Becoming an Immunologist

My first exposure to immunology was through my Ph.D. with Ian McKenzie at the University of Melbourne; we were modifying antibodies—coupling drugs and toxins—and measuring their activity in mouse models of transplantation and cancer. As a next step, I wanted to learn molecular biology. I did the typical Australian thing and interviewed at laboratories across the U.S., and the U.K., but I chose NCI's Biological Response Modifiers Program in Frederick, Md., based on its collaborative feeling.

I started working with John Ortaldo, Ph.D., on a very tough project to isolate a cytotoxic factor secreted by NK cells. After six months, a couple of really good colleagues took me aside and said I ought to find a back-up project. That's how I began working with Howard Young, Ph.D. (now Deputy Chief of CCR's Laboratory of Experimental Immunology). Despite leaving John's lab formally, John remained a really good friend and mentor.

In Howard's lab, we studied the transcriptional control of pore-forming protein, a.k.a. perforin, a cytotoxic molecule in mammalian lymphocytes and a major pathway by which they kill target cells. We published our results demonstrating how interleukin-2 (IL-2) activates the killing machinery of these lymphocytes. And we discovered that TGFβ suppresses perforin activation, which has had lasting importance for tumor immunology.

I became skilled at Northern blots, which enabled me to initiate many projects with other people. Howard gave me a lot of independence, and his lab was very interactive. Up the hall, we had a new young investigator, John J. O'Shea, M.D. (now Scientific Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases), with whom I published on the pervanadate method to study phosphatase function. Through golf, I met a younger team leader, Kouji Matsushima, Ph.D. (now Professor at the University of Tokyo in Japan), with whom I collaborated on chemokine production in NK cells.

At the end of my time in Frederick, I had morphed into an immunologist.

On Building a Career

When I returned to Australia, I joined the Austin Research Institute and started working with Joe Trapani, Ph.D., on perforins. Eventually, I decided to go back to biology, which interested me more than the cellular mechanisms. I had become very interested in immune surveillance. Was the immune system continuously getting rid of cancerous cells? This idea had been around since Frank Macfarlane

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Burnet, M.D., and Lewis Thomas, M.D., proposed it in the 1950s, but it's an impossible concept to demonstrate in humans precisely. Suggestive examples exist, such as patients who develop malignancies after receiving organs from a "cured" donor.

We reasoned that if perforins were important for the immune response to cancer, then mice lacking perforin must have a higher probability of developing tumors. So we engineered mice that were both p53 deficient (i.e., prone to cancer) and perforin knockouts. We saw that lymphomas developed earlier and were more prevalent in mice lacking perforin. We continued to use this approach with other molecular components of the immune system. We have accumulated over 100 genetically modified mice that now serve as a platform for investigating which host molecules are important in controlling tumor growth.

We also used an older model of cancer as a platform: the chemical carcinogen, 3-methylcholanthrene (MCA) injected into the flank, in various immune-deficient backgrounds. Some of the experiments would take a year or more to do, because the tumors were slow growing. But for studying immune surveillance, we felt it was a much more realistic model of cancer progression than, for example, tumor transplants.

On Cancer Immunoediting

In 2000, Lloyd Old, M.D., sometimes called the "Father of Modern Tumor Immunology" invited me to a meeting in New York. From that meeting sprung a fabulous collaboration with Robert Schreiber, Ph.D., at Washington University in St. Louis, Mo. Bob proposed the cancer immunoediting concept, now a cornerstone of thinking about how the immune system reacts with cancer. Because tumors are genetically unstable and the immune system is exerting selection pressures constantly, tumors eventually develop immunoresistant clones.

Immunoediting posits an equilibrium phase, during which the immune system and the tumor go into battle. We found we could describe a phase of tumor dormancy mediated by the immune system with the MCA model. When we injected low doses of carcinogen, the host formed a granuloma, a localized inflammatory response. These lesions eventually disappeared with time. But when we depleted the immune response, 60–70 percent developed fast growing sarcomas at the site of the original injection. We were able to track those tumors and show some cells within had malignant potential. We published that paper in *Nature* in 2007.

We continue to try and understand the equilibrium phase, what kind of sculpting is going on, what drives tumors to escape, whether you can bring them back to an equilibrium. If so, you might have a way of making cancer a chronic disease without necessarily curing it.

On Clinical Translation

As we've been able to understand escape mechanisms and pathways, we're increasingly interested in preclinical models for therapeutic development.

About 10 years ago, with our colleagues in Tokyo, we tested the concept that combinations of antibodies could increase therapeutic benefit. Now, it may seem obvious, but at the time, we were staggered by synergy we saw between antibodies that blocked the TRAIL receptor to stimulate apoptosis and antibodies that stimulated dendritic cell and T-cell activation. It was very satisfying to see the combination of ipilimumab (an antibody against CTLA-4) and nivolumab (an antibody against the PD-1 receptor) in a successful phase 1 trial for advanced melanoma published in the *New England Journal* two years ago.

We are currently pursuing another surface protein—CD96—which we discovered inhibits lymphocytes' ability to attack cancer cells. We were just awarded a grant to screen a series of antibodies against this target for use in a clinical trial.

It's an exciting time for immunotherapies. There's been a lot of background work that is going to come to fruition. It has been surprising people in the field how well anti-PD-1/PDL1 have worked. Approaches that have been tried and failed might have new value. We're just scratching the surface and T cells are just part of the story. There is a lot of opportunity to mobilize other cell types. Moreover, we need to recognize that patients will have their own unique antigens. We will need to stratify human tumors to match patients with the right treatment strategies.

These are really hard problems and the value of collaboration can't be underestimated. I am incredibly grateful for the postdoc period I spent in Frederick. It taught me to be a great collaborator, it really accelerated my career, and I've kept friendships with the people I met along the way.